Nutrition 78 (2020) 110829

Contents lists available at ScienceDirect

Nutrition

journal homepage: www.nutritionjrnl.com

Applied nutritional investigation

Assessing successful completion of calorie restriction studies for the prevention and treatment of cancer

Colin E. Champ M.D., CSCS [a,*], Rainer J. Klement Ph.D [b]

[a] Duke University Medical Center, Department of Radiation Oncology, Durham, North Carolina, USA
[b] Leopoldina Hospital, Department of Radiation Oncology, Schweinfurt, Germany

ARTICLE INFO

Article History:
Received 6 January 2020
Received in revised form 6 March 2020
Accepted 16 March 2020

Keywords:
Calorie restriction
Cancer
Cancer prevention
Diet and cancer
Cancer treatment

ABSTRACT

Objectives: Calorie restriction (CR) >20% has been hypothesized to aid cancer prevention and treatment. Yet, to our knowledge, there is a lack of reported studies in humans describing tolerance, adherence, or efficacy, and unpublished and incomplete dietary studies may indicate lack of tolerability and compliance. The aim of this study was to assess registered clinical trials using CR for cancer treatment and prevention, rates of completion, and published reports to determine whether barriers to publication may be indicative of either negative studies, or incompletion due to unreported compliance issues.
Methods: Current registered clinical trials assessing CR in cancer prevention and treatment were assessed at clinicaltrials.gov and the International Clinical Trials Registry at the World Health Organization. Assessment of study completion and publication was calculated and compared with methods of CR used, as were rates of inactive and incomplete studies, dormant studies, time of dormancy, type of study, and generalizable conclusions.
Results: Twenty-nine trials were registered assessing CR in cancer treatment or prevention. Of these studies, 18 met initial criteria, and only 4 had completed and published results. Three of these tested a CR regimen incorporating exercise or intermittent restriction. Target CR ranged from 500 to 1000 kcal/d, with one study aim of 20% CR; no study reported rates of actual calorie intake. The majority of dormant and unpublished studies (69%) used general dietary CR and was without update ranging from 265 to 2518 d. Only one study reported on the side effects of the CR regimen; compliance and adherence to the regimen was described in the four completed studies that reported results. Only two studies were registered as pilot studies testing the feasibility of CR.
Conclusions: Poor completion and lack of reporting of results is apparent in the majority of studies assessing CR for cancer prevention or treatment. These findings should be considered during the design of future studies assessing dietary strategies for cancer prevention or treatment.

Introduction

Rates of obesity-related malignancies and general obesity in patients with cancer continue to rise at an alarming rate [1]. Increased cancer risk and poorer outcomes have been associated with both obesity and obesity-related diseases like insulin resistance and metabolic syndrome [2–5]. In response to these findings, combating weight gain and promoting weight loss during or after cancer treatment have been recommended in an effort to improve outcomes [6]. This would conform to preclinical studies revealing that overall calorie restriction (CR), specific nutrient restriction, or a combination of both, can improve outcomes of cancer treatment and may aid in cancer prevention [7,8]. For example, both CR and alternate-day fasting increased efficacy of radiation therapy against mammary tumors in a mouse model [9].

However, the bulk of preclinical studies have required calorie deprivation between a 20% and 40% restriction of daily intake [7]. Along the same lines, dietary recommendations for patients with cancer and the general population to achieve weight loss generally endorse a calorie reduction of 500 kcal/d, which also fits within the 20% to 40% reduction for much of the general population [10].

Compliance, a vital component of diet and lifestyle recommendations, has generally been poor in published studies [11].

CEC was responsible for data curation, analysis, methodology, original draft, and editing. RJK was responsible for data curation, analysis, methodology, and editing. CEC receives compensation for health-related books and is a director of the nonprofit Advancing Ketogenic Therapeutics, which funds studies pertaining to diet and cancer. RJK has no conflicts of interest to declare.

*Corresponding author. Tel.: +1 919 660 2100, Fax: 1 919 6687345
E-mail address: Colin.Champ@Duke.edu (C.E. Champ).

https://doi.org/10.1016/j.nut.2020.110829
0899-9007/

Although preclinical research on CR has shown promise, it has been generally limited to mice, posing the question whether humans in real-world settings are able to engage in similar calorie deprivation. Two initial studies assessing CR in noncancer populations, the Minnesota SemiStarvation Experiment and Biosphere 2, resulted in significant morbidity, although this was unreported in the published studies on the intervention [12–14]. In a modern CR study, individuals randomized to 6 mo of 25% CR lost weight, but were only able to reduce their calories by 15% [15]. A larger multisite study, the CALERIE (Comprehensive Assessment of Long-term Effects of Reducing Intake of Energy) trial, attempted 25% CR over 2 y and achieved an average restriction of 11.7% ± 0.7% of calories over the study duration [16]. Neither study commented on the tolerability of the diet or side effects experienced by participants.

To our knowledge, no studies to date have achieved their prescribed CR goal. Although voluntary CR to about 1100 to 2000 kcal/d over several years has been observed for a few highly motivated individuals, corresponding to about 30% restriction compared with a Western diet [17], the poor compliance by participants in the few published clinical trials raises concerns of compliance of CR recommendations in the general population. This gap in the literature is worrisome, as many recommendations promote similar CR for health improvement, yet weight loss from CR at the recommended levels described previously can lead to muscle loss and decreased bone density [18]; both are concerning changes within the cancer setting.

This lack of discussion on the safety and tolerability of CR in the cancer setting led us to evaluate the current state of clinical trials assessing CR and completion rates and to hypothesize whether barriers to publication may be indicative of either negative studies, or incompletion due to unreported compliance issues.

Method and materials

Current clinical trials pertaining to CR and cancer prevention and treatment were assessed via an unregistered systematic review of the clinical trials registry at clinicaltrials.gov and the International Clinical Trials Registry Platform at the World Health Organization (WHO). These online sources track all submitted research trials and accompanying data, including the status of the trial, number of patients enrolled, outcome measures, the study start and completion date, posting of resulting papers, date of posted results, and several other specific outcome-related measures. The trial databases were searched from their inception until November 22, 2019, using the search terms "all studies" for status, "cancer" for condition or disease and "calorie restriction" for other terms; country was left blank to include all studies. Studies were only included if they assessed a CR eating pattern in individuals diagnosed with cancer, or as a cancer preventative mechanism in individuals without cancer or with previously treated cancer and now in remission (PRISMA flowchart in Fig. 1). A search for any additional manuscripts published from the listed trials in clinicaltrials.gov, but not listed on this trial platform, was performed with MEDLINE and PubMed. Furthermore, to ensure publications from the proposed study did not exist, the listed primary author's name was searched on PubMed and all available studies were tabulated and assessed. Lastly, a search was performed via PubMed and MEDLINE for any clinical trials not listed on clinicaltrials.gov or the WHO database but producing publications on cancer treatment and prevention using CR.

Results were tabulated and compared via descriptive statistics. Assessment of successful study completion and publication was calculated, as were rates of inactive and incomplete studies, dormant studies, time of dormancy, type of study, and generalizable conclusions. These findings were then compared with methods of CR used, including general CR, intermittent restriction, exercise, or a combination. Risk for bias was not assessed owing to the small amount of completed studies.

Results

Twenty-nine clinical trials were registered with ClinicalTrials.gov and 1 was registered with the WHO database. Of these, 18 met initial criteria and assessed a calorie-restricted dietary eating pattern in patients with cancer or as cancer prevention (Fig. 1). At the time of database search, only four studies had published their results (Table 1). Four studies had reached completion status, yet were lacking existing published studies of the findings and without report from the study (Table 2). Of note, one of the studies only completed 268 d ago. Of the remaining studies, several appeared to be dormant. Three were listed as active but were not recruiting and have not been updated for 265, 470, and 2518 d. An additional study was listed as unknown for 1453 d, and one was listed as not yet recruiting for 1265 d. No further studies assessing CR for cancer prevention or treatment were found with the additional database searches.

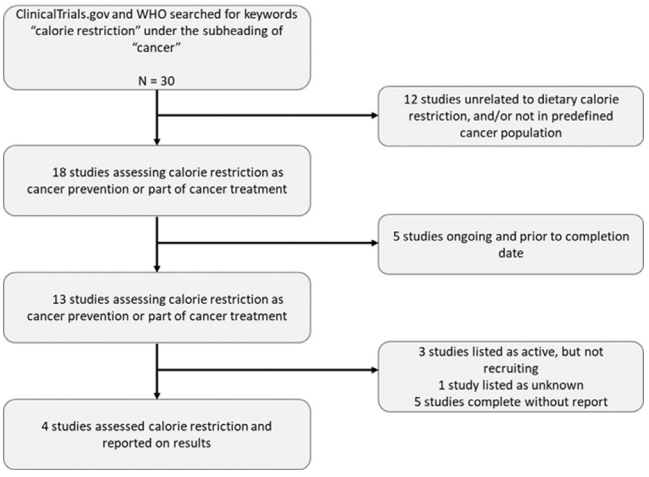

Fig. 1. Study search results and flowchart. WHO, World Health Organization.

Only 1 of 18 studies reported on the side effects of the calorie-restricted regimen tested [19]. These were generally minor and included mild cognitive impairment, lack of concentration, feeling cold and tired, and having mild headaches. Compliance and adherence to the dietary regimen was described in the four studies that reported results [19–22]. One of these used patient logs to calculate compliance [19], whereas the other three defined compliance via participant group meeting attendance. Only two studies were registered as pilot studies to test the feasibility of CR. One of these posted results [22], whereas the other has not posted an update in 6 y. The target CR prescription in the completed studies ranged from 500 to 1000 kcal/d, with one study goal of 20% CR, yet to our knowledge, no study calculated or reported actual rates of CR at study completion.

Of the four studies that completed and reported results, only one tested an isolated general calorie-restricted dietary regimen, and this study included CR with the addition of an exercise arm (Table 1) [21]. Two of the completed studies used mixed dietary and exercise regimens to achieve CR [20,22], and one used a regimen with 2 d of a 25% intake and then 5 d with normal calorie intake (known as a 5:2 regimen) [19]. All four studies were testing CR in an effort to improve metabolic variables and in the preventative setting. The results of these studies are listed in Table 3. Of the 13 unpublished not accruing studies, 9 (69%) contained one intervention arm testing overall CR through diet alone (Table 2).

Discussion

Findings from the present review illustrated limited completion and reporting of findings of registered CR studies for cancer prevention or treatment. Such findings are novel, as negative or unpublished studies most commonly go unnoticed within the medical community, and this information is important for future clinical trial design.

Table 1
Calorie restriction studies with reported results

Study	Patient cohort	Intervention	Specifics	Length	Participants	Ages (y)	Date comp.	Measurement	Side effects	Compliance	Compliance measured	Other findings
Nutrition and Energy Restriction for Cancer Prevention (HELENA)	Obesity and metabolic disease	CR	ICR: 2 d with 25% calorie intake, 5 d with 100% calorie intake (5:2) or General CR: 20% CR	24 wk	150	35–65	May 2017	Array of tests*	Several minor effects listed	ICR: high at week 7, 32.6% at week 24, 21.4% week 50, CCR unreported	Journals	Significant CR from protein reduction
Weight Loss Pilot Study in Postmenopausal Breast Cancer Survivors	Breast cancer	CR + exercise	Daily meals and exercise to achieve 1000 kcal restriction	12 wk	22	44–75	August 2010	Change in body weight	NR	77.50%	Number of sessions attended	
Effect of a Low-Calorie Diet and/or Exercise Program on Risk Factors for Developing Breast Cancer in Overweight or Obese Postmenopausal Women	Overweight/obese at risk for breast cancer	CR ± exercise	Low-calorie diet and/or exercise program (unclear but with aim of 10% weight loss)	6 mo	439	50–75	February 2010	Array of tests†	NR	In both groups, women attended an average of 27 diet counseling sessions (86%)	Logs, weekly weigh-ins, pedometer steps, and session attendance	
The Effects of Equivalent Weight Loss With or Without Exercise Training on Breast Cancer Risk (SHAPE-2)	Breast cancer	CR ± exercise	Dietary 500 kcal or dietary 250 kcal and exercise 350 kcal	14 wk	250	50–69	October 2014	Changes estradiol (total, free), estrone, testosterone, sex hormone binding globulin, changes in BMI, weight, waist and hip circumference, total body fat (DXA scan), abdominal fat (subcutaneous and visceral, MRI-abdomen) and physical fitness (maximal exercise capacity test by the ramp protocol).	NR	Adherence defined as >80 %. Drop-out rate low at 5%. Median number of diet group sessions attended was 4 (out of 5 offered) and 70% of women attended ≥4 sessions. No comments on whether calorie deficit achieved	3-d food diaries, exercise log, self-weighing performed weekly (in diet group) or biweekly (in exercise group), frequent contact	CR with exercise appeared better

BMI, body mass index; CR, calorie restriction; CCR, chronic calorie restriction; DXA, dual-energy x-ray absorptiometry; ICR, intermittent calorie restriction; comp., complete; MRI, magnetic resonance imaging; NR, not reported.
*Changes in abdominal fat distribution pattern; blood-based biomarkers; the composition of the gut microbiota by taxonomic, functional, and comparative analysis of sequencing data; blood, leukocyte, and urine metabolites; weight, BMI, waist and hip circumferences; blood pressure and pulse; quality of life; and liver fat content measured by magnetic resonance spectroscopy.
†Changes in serum estrone concentrations, serum estradiol, and free estradiol concentration; testosterone and free testosterone as measured by radioimmunoassay; serum concentrations of sex hormone binding globulin; mammographic density measurements; weight and BMI; total and percentage body fat and body fat distribution; quality of life, daily calorie intake; leukocyte and neutrophil counts; serum concentrations of insulin as measured by radioimmunoassay; serum concentrations of glucose; serum concentrations of insulin-like growth factor-1; serum concentration of nsulin-like growth factor-binding protein-3; serum vitamin D concentrations; serum ghrelin concentrations as measured by radioimmunoassay; serum C-reactive protein concentrations; serum concentrations of amyloid A; serum interleukin-6; serum adiponectin concentrations; serum leptin concentrations; serum androstenedione concentrations; and serum c-peptide concentrations.

Table 2
Unreported, incomplete, and dormant calorie restriction studies

Study	Status	Conditions	Intervention	Intervention details	Intervention length	Participants	Ages (y)	Time since completion (d)	Time since update (d)	Measurement	Results posted	Others
Energy Balance Interventions for Colorectal Cancer Prevention	Completed	At risk for colon cancer	CR, exercise, CR + exercise	Unclear	Unclear	40	50+	2367	n/A	Physical activity-energy expenditure, dietary-energy intake and quality, body weight and composition	No	
Calorie-restricted, Ketogenic Diet and Transient Fasting During Reirradiation for Patients With Recurrent Glioblastoma (ERGO2)	Completed	GBM	Days 1–3 and 7–9, restriction of carbohydrates <60 g and of calories to 21–23 kcal•kg•d^{-1}, on days 4–6 fasting	On days 1–3 and 7–9, restriction of carbohydrates can be supported by the use of drinks provided by "Tavarlin."	6 mo	50	18+	268	n/A	PFS, OS, seizure frequency, feasibility, safety and tolerability, urine and blood ketones, QoL, depression scores, attention scores, response scores	No	Recently completed
DIetary Restriction as an Adjunct to Neoadjuvant ChemoTherapy for HER2 Negative Breast Cancer (DIRECT)	Completed	Breast cancer undergoing NAC	FMD	Very low calorie, low amino acid substitution diet (FMD)	Unclear	131	18–70	388	n/A	Toxicity, rate of pCR, clinical response on MRI, side effects of chemotherapy, glucose, IGF-1, IGFBP-3, free thyroxin, triiodothyronine and TSH, CRP, DNA damage, apoptosis, QoL, burden of therapy, differences of illness perceptions, DFS, OS, hormone receptor percentage, Ki67, immunologic tumor profile, tumor/stroma ratio, outcome biomarkers	No	
Dietary Intervention and BRCA Penetrance	Unknown (listed as completed 2018)	Breast cancer risk	CR	Reduce protein intake from milk and animals (except fish) to 10%–12% of total calories. Reducing high glycemic index/ insulinemic foods. Reducing sources of saturated fat (red and processed meat, milk and dairy products). Eating mostly food of plant origin, with a wide variety of seasonal products.	6 mo	600	18–70	n/A	998	Change in serum IGF-I, comparison of the affected vs the unaffected *BRCA* mutation carriers with serum IGF-1, breast cancer incidence	No	Author-published study with 348 *BRCA*-mutated women. 54 women dropped out before baseline examinations and randomization. No comment on trial
Caloric Restriction Before Surgery in Treating Patients with Endometrial, Prostate, or Breast Cancer	Active not recruiting	Breast, endometrial, or prostate cancer	CR	25% caloric intake	3–12 wk before cancer surgery	49	18+	n/A	265	Change in serum mRNA 21 expression and adherence to the diet, prostate tumor gene expression, weight, temperature, insulin, biome analysis assessed by rectal swab, psychosocial outcomes, nutritional status, local recurrence, distant metastases, PFS, OS, blood pressure, heart rate, respiratory rate, psychosocial outcomes, assessed by the FACT-P, psychosocial outcomes	No	

(*continued on next page*)

Table 2 (*Continued*)

Study	Status	Conditions	Intervention	Intervention details	Intervention length	Participants	Ages (y)	Time since completion (d)	Time since update (d)	Measurement	Results posted	Others
Effect of a Clinical Nutrition Intervention Program in Breast Cancer Patients During Antineoplastic Treatment	Active, not recruiting	Breast cancer	CR	CR (500−1000 kcal/d) if needed, plus an array of dietary recommendations	6 mo	44	18+	n/A	470	Change in BW, body fat, fat-free mass, skeletal muscle mass, waist circumference, retinol, Trolox-equivalent antioxidant capacity test, glutathione peroxidase, superoxide dismutase, human inflammatory cytokines	No	
Ketogenic Diet as Adjunctive Treatment in Refractory/End-stage Glioblastoma Multiforme: a Pilot Study (KGDinGBM)	Active, not recruiting	GBM	KD and CR	KD will consist of 4:1 fat:protein + carbohydrate weight ratio with 1600 kcal restriction and supplemented with vitamins, calcium, phosphorus, zinc, and selenium supplements to meet the requirements of US Dietary Reference Intakes (standard.	6 mo	6	18−65	n/A	2518	Safety of KD, treatment, early treatment discontinuation, treatment compliance, 7-point Licker hunger scale, fasting lipid levels and fasting serum glucose and insulin levels, OS, time to steroid requirement, tolerability, incidence of treatment-emergent AEs during treatment	No	
Effect of Daily Calorie or Alternate-day Calorie Reductions on Risk for Cardiovascular Disease and Cancer	Unknown	Moderately overweight individuals	CR	CR or ADF (no specifics)	12 wk	40		n/A	1453	Adipose tissue dynamics (triacylglycerol turnover, lipolysis, de novo lipogenesis, adipose cell proliferation), adipose tissue morphology (cell size and number), adipose tissue hormone levels (adiponectin, leptin), skin turnover (keratin dynamics), T-lymphocyte proliferation, plasma lipid and lipoprotein, homocysteine, and CRP level	No	
Effects Of Caloric Restriction On PostOperative Complications In Sarcoma Patients Treated With Pre-Operative Radiation Therapy	Not yet recruiting	Sarcoma	Calorie reduction to 30%. Protein needs estimated at 0.8 g/kg BW and then reduced by 70%	Nutritional supplement used for 3 d before surgery (45% fat, 46% carbohydrate, and 8% protein)	3 d	30	18+	n/A	1265	Change in physical function, Musculoskeletal Tumor Society Rating Scale, Toronto Extremity Salvage Score, rate of wound healing, rate of wound complications	No	

ADF, alternate-day fasting; AE, acute event; BW, body weight; CR, calorie restriction; CRP, C-reactive protein; DFS, disease-free survival; FMD, fasting mimicking diet; GBM, glioblastoma multiforme; IGF, insulin growth factor; IGFBP, insulin-like growth factor binding protein; KD, ketogenic diet; MRI, magnetic resonance imaging; n/A, not associated; NAC, N-acetylcysteine; NR, not reported; OS, overall survival; pCR, pathologic complete response; PFS, progression-free survival; QoL, quality of life; TSH, thyroid-stimulating hormone.

Table 3
Results of trials that reported on calorie restriction

Method	Calorie change (%)	Weight loss (%)	Glucose (%Δ)	Insulin (%Δ)	HOMA index (%Δ)	IGF-1 (%Δ)	IGFBP-3/ SHBG (%Δ)	Leptin (%Δ)	Adipo. (%Δ)	CRP (%Δ)	IL-6 (%Δ)	Cortisol (%Δ)	Estrone (%Δ)	Estradiol (%Δ)	Test. (%Δ)	PAI-1 (%Δ)	PEDF (%Δ)	VEGF (%)	Ref.
CR	ICR: −34.5* CCR: −25.4 CT: −9.8	ICR: −7.1* CCR: −5.2 CT: −3.3	ICR: −2.9* CCR: −7.6 CT: −5.2	ICR: −6.3* CCR: −19.3 CT: −9.1	ICR: −9.0* CCR: −27.1 CT: −14.3	ICR: 11.7* CCR: 3.4 CT:2.5	n/A	ICR: −47.9* CCR: −48.4 CT: −44.3	ICR: −5.2* CCR: −7.5 CT: −7.9	ICR: −17 CCR: −24.5 CT: −25.1	ICR: +5.6 CCR: +12.1 CT: +6.6	n/A	PM: ICR: −21.8 CCR: +10.1 CT: −8.2 M: ICR: +11.7 CCR: +9.1 CT: +13.2 Male: ICR:-10.3 CCR: −10.7 CT: −11.6	n/A	Female: ICR: +0.7 CCR: +1.8 CT: −12.7 Male: ICR: −4.4 CCR: +4.9 CT: −5.2	n/A	n/A	n/A	19
CR + Exercise vs. WM	n/A	CR: 9.3 WM: 4.3	CR: −6.4 WM: −4.3	CR: −33.3 WM: −29.9	CR: −38.9 WM: −40.7	CR: +4.1 WM:+1.3	CR: −3.4 WM: −4.6	CR: −59.6 WM: −31.6	CR: +13.3 WM: +2.6	CR: +46.7 WM: +42.3	CR: −18.5 WM: −17.9	CR: −2.7 WM: −10.4	n/A	n/A	n/A	n/A	n/A	n/A	22
CR +/- Exercise, Exercise alone, vs CT	CR: −13 E: −9.3 CR+E: −14 CT: −11	CR: −8.5† E: −2.4 CR+E: −10.8 CT: −0.8	CR: −2.4† E: −0.9 CR+E: −2.8 CT: +0.2	CR: −22.3† E: −7.8 CR+E: −24 CT: −1.9	CR: −24.3 E: −8.6 CR+E: −26.4 CT: −1.8	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A	n/A	CR: −9.3† E: +8.2 CR+E: −19.3 CT: +3.48	CR: −9.2† E: −2.6 CR+E: −9.9 CT: 0.2	CR: −1.2† E: −8.3 CR+E: −3.1 CT: −10.0	21
CR ± exercise	n/A	CR: −5.4† CR+E: −4.3	n/A	n/A	n/A	n/A	CR: +12.6 CR+E: +19	CR: −41 CR+E: −45.1	CR: −0.3 CR+E: 1.79	CR: −12.3* CR+E: −26.1	CR: −6.8 CR+E: −5.7	n/A	CR: −13.8 CR+E: −12.7	CR −13.8 CR+E: −12.7	CR: −3.8 CR+E: −7.6	n/A	n/A	n/A	20

Adipo, adiponectin; BMI, body mass index; comp, complete; CR, calorie restriction; CCR, chronic calorie restriction; CT, control; DXA, dual-energy x-ray absorptiometry; HOMA, homeostasis model assessment; ICR, intermittent calorie restriction; IGF, insulin-like growth factor; IGFBP, insulinlike growth factor binding protein-3; kcal, kilocalorie; M, menopausal; MET, metabolic equivalent of task; MRI, magnetic resonance imaging; n/A, not assessed; NR, not reported; PAI, plasminogen activator inhibitor; PEDF, pigment-epithelium-derived factor; PM, premenopausal; ref, reference; SHBG, serum hormone binding globulin; test, testosterone; VEGF, vascular endothelial growth factor.
*Loge relative change.
†Statistically significant.

These findings are consistent with other reviews of published studies assessing dietary restriction strategies during cancer treatment, which frequently include few patients and are described as well tolerated, although adherence is variable [23]. Most of the currently available studies are retrospective, and the majority have assessed a ketogenic diet, followed by fasting, protein restriction, and mixed interventions. There are no studies assessing general CR as part of these published studies. Incorporating the large number of uncompleted and unpublished studies within these nominal findings provides serious concerns regarding the ability of humans to withstand any significant CR regimen, but especially those that aim to prevent cancer or aid in its treatment.

Although the overall number of completed and published studies is small, it is notable that the more recent studies that are currently underway tended to promote short-term CR or exercise regimens before chemotherapy treatment. We found that the majority of incomplete and unpublished studies assessed general CR, whereas the published studies included exercise or a 5:2 regimen to achieve a calorie deficit. Consideration of these findings, and the previously published results described earlier, may suggest that the latter approach is more tolerable and less toxic to participants. Methods to promote compliance to restricted diets are vital, as the studies that completed and reported on their findings found several significant changes associated with oncologic benefits in breast cancer treatment and prevention. For instance, the benefits described in Table 3 reveal that weight loss was achieved in overweight individuals who successfully limited their calories. Furthermore, impactful metabolic changes were achieved, including reduced insulin, glucose, and C-reactive protein, all of which are associated with a lower risk for cancer [24,25]. The serum biomarkers for angiogenesis, including vascular endothelial growth factor, plasminogen activator inhibitor-1, and pigment-epithelium-derived factor were significantly decreased [26]. Finally, calorie-restricted participants also experienced reductions in serum estrogens, which could be significant in individuals treated for hormone receptor−positive breast cancer [19,20].

Perhaps most concerning with the present findings is that dietary recommendations commonly recommend a 500 to 1000 kcal/d reduction via a general restriction of calories [27]. Poor compliance by participants in the clinical trial setting raises significant concerns of compliance for the general population. It is unclear what the optimal recommendations should be, but it is notable that studies have revealed that certain foods and recommendations may affect caloric consumption. A recent randomized controlled trial revealed successful weight loss without purposeful CR, but instead via the promotion of high nutrient density and food quality instead of quantity [28]. Furthermore, a study revealed that processed and ultra-processed foods, when matched with non-processed foods for calories, sugar, fat, fiber, and macronutrients, promote the spontaneous consumption of increased calories [29]. Several studies comparing carbohydrate restriction without CR versus low-fat calorie-restricted diets have revealed a similar reduction in calories, suggesting that single macronutrient reduction may be an acceptable and tolerable approach for some individuals to successfully reduce their calories [30,31].

Finally, many preclinical studies have shown promise regarding cancer prevention or treatment when specific pathways are targeted via dietary changes, including the insulin pathway, phosphatidylinositol 3-kinase, AKT, and insulin growth factor-1 [7]. Coincidentally, many of these pathways may be readily targeted via specific macronutrient restriction and other dietary approaches that may be more tolerable than long-term or severe CR [32,33]. the present review had several limitations. Clinictrials.gov is a registered database, but details for the poor publication and follow-through of the studies described here are not provided, limiting conclusions. Additionally, interest in dietary manipulation and cancer has recently increased, so there may be a delay in studies to catch up with this enthusiasm. However, as the results of negative and unpublished studies rarely become known in the scientific field, assessing the specifics of these studies, especially when they are testing current recommendations, is an important approach to improve recommendations and future studies.

Conclusions

Current registered studies assessing CR in the oncology setting have poor rates of follow-through and completion, with the majority remaining unpublished and unreported. Although the reasons for incompletion of the proposed studies is unknown due to lack of publishing, these findings are concerning in that they may indicate poor compliance or excessive toxicity. Until further studies are produced, evidence of the tolerability and effect of CR in the oncology setting remains limited. Future studies and dietary recommendations for patients with cancer should consider these findings and tolerability of diets.

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